NOTES

Effect of Blending Methyl β-Cyclodextrin on the Release of Hydrophobic Hydrocortisone into Water from Polyurethane

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INTRODUCTION

Sustained drug release from polymeric matrices has been studied vigorously through the years.[1–3] The benefits of retarded drug release from polymers are well known. Several drugs having therapeutic values are hydrophobic in nature, and their solubility in aqueous fluids are very low and often fall below the concentration needed. In such cases, different approaches mainly the incorporation of other agents along with the drugs have been attempted.[4,5]

Cyclodextrins, the oligomers of glucose, are well known for their ability to form inclusion complexes with a variety of components.[6,7] These cylinder-shaped molecules have extensively been used in pharmaceutical and related applications.[8,9] Methyl beta cyclodextrin (MCD), a derivative of β-cyclodextrin, has interesting properties. This compound is highly soluble in both aqueous and nonaqueous media. The MCD is known to enhance the water solubility of hydrophobic compounds like steroids.[9] It would be interesting to investigate the release of hydrophobic entities from an MCD containing polymeric matrix into water. Such study, as far as this investigator knows, has not been reported. The present communication discusses the release of a model drug, hydrocortisone, into water from a polyurethane matrix containing MCD.

EXPERIMENTAL

Polyurethane (PU) used in this study was based on polytetramethylene glycol (Molecular weight 1000), 1,4-bis(p-cyclohexyl isocyanate) and 1,4-butane diol. The PU containing 22% hard segment content was prepared by a two-stage process as reported elsewhere.[10] Methyl β-cyclodextrin and hydrocortisone were obtained from Sigma Chemicals Co., St. Louis, MO, USA. Other chromatographic or analytical grade reagents were procured from Spectrochem, Bombay, India.

Preparation of the Drug Containing Matrix

Appropriate amounts of PU, MCD, and hydrocortisone (Hy) were dissolved in tetrahydrofuran. A film was prepared by slowly evaporating the solvent from a petri dish at room temperature (30°C). The film was then kept in a vacuum oven at 70°C for 24 h to remove the traces of the organic solvent. In a similar fashion, films containing only MCD and Hy were also prepared.

Release of Hy from the Matrices into Water

Films having an area of 2 cm^2 and a thickness of 1 mm were placed in 25 mL double distilled water at room temperature (30°C) with occasional stirring. At regular time intervals, 100 μL of the samples were drawn and analyzed chromatographically to estimate the quantity of Hy released.

Estimation of the Total Hy in the Films

The film was dissolved in tetrahydrofuran and the polymer was precipitated by adding methanol. The filtrate

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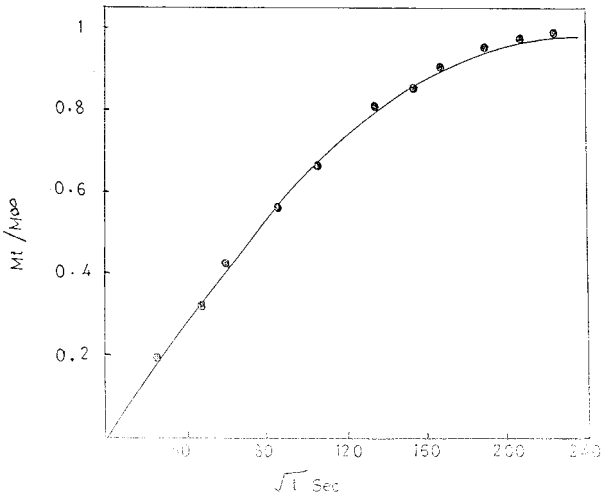

Figure 1 Mt/M_∞ vs $t^{1/2}$ plot of Hy in PU.

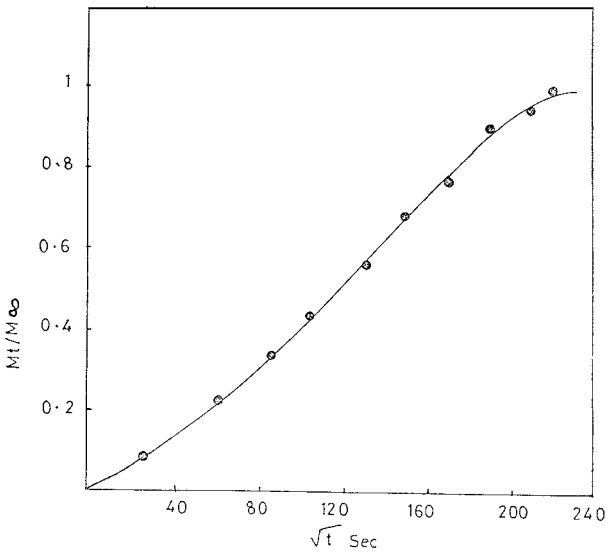

Figure 2 Mt/M_∞ vs $t^{1/2}$ plot of Hy in PUCD.

was collected. The precipitate was washed three times with methanol and the combined filtrate was evaporated to dryness. The residue was dissolved in acetonitrile and analyzed chromatographically to estimate the quantity of Hy.

Estimation of MCD in the Polymer Matrix

As mentioned above, the polymer was removed and the filtrate was dried. The residue was dissolved in water and the MCD was estimated using alkaline phenolphthalein as reported elsewhere.[11]

Instrumental

A Waters Associates, Inc. (Milford, MA, USA), High Performance Liquid Chromatographic system consisting of a model 410 solvent delivery pump, 2725 Reodyne injector, and 486 tunable absorbance detector was used for the chromatographic analysis. A μ-bondapak C_{18} column (Waters Associates, Inc.) in conjunction with acetonitrile as mobile phase at a flow rate of 1 mL/min was employed for the separation and estimation of the drug. The column effluents was monitored at 241 nm. A calibration plot was constructed between peak heights and the corresponding quantity of standard solutions of Hy. This plot was used for the quantification of Hy released from the matrices.

RESULTS AND DISCUSSION

Figure 1 shows the release profile of Hy with time from PU. Figure 2 depicts the time dependent release of Hy from PU containing MCD (hereafter PUCD). The diffusion coefficients commuted from the relation

$$S = 4/1(D/II)^{1/2} \quad (1)$$

where S is the slope of the linear portion of the trace, l is the thickness in centimeters, and D is the diffusion coefficient. The D values estimated from eq. (1) are summarized in Table I. It is interesting to see that D of Hy from PUCD is considerably higher than that of the D of Hy in PU.

MCD is highly soluble in water. When the PUCD matrix comes in contact with water, dissolution of MCD into water commences from the surface of the polymer matrix. The concentration gradient, established as a result of the dissolution, enhances the migration of the MCD from bulk of the material to the surface and then into water. Since the MCD is a relatively big molecule, its migration from bulk to surface is rather slow. Additionally, the hydrophobic nature of PU prevents the diffusion of water molecules into the bulk to enhance the dissolution of MCD. Largely due to these aspects, the rate of dissolution of MCD into water is remarkably less from PU. The quantity of MCD migrated into water at different time intervals is shown in Table II. It can be seen that after 24 h, the extent MCD dissolved

Table I Diffusion Coefficients of Hy in PU and PUCD Matrices

Component	Diffusion Coefficient (cm^2/s)
Hy in PU	1.66×10^{-9}
Hy in PUCD	6.16×10^{-9}

Table II Time-Dependent Release of the Components into Water

Time (h)	MCD Diffused into Water (mg)	Hy Diffused into Water from PU (mg)	Hy Diffused into Water from PUCD (mg)
2	2.07	0.15	0.7
6	3.02	0.45	1.03
12	3.72	0.65	1.19
24	4	0.69	1.23

is just 4 mg, which is only 25% of the total MCD present in the polymer matrix. The solubility of MCD in water is 100 g/100 mL.[9] The low rate of migration of MCD into water, comparing to the substantial solubility of free MCD in water, could possibly be traced to the above-mentioned aspects.

Table II also summarizes the time related Hy dissolution from PU and PUCD matrices. It is interesting to see that the extent of Hy dissolution into water from the PUCD matrix is significantly higher than the quantity of Hy released from PU matrix. Apparently the data suggest the strong influence of MCD blended with the PU.

The enhanced dissolution of Hy from PUCD matrix comparing to PU matrix can be attributed to the presence of MCD in water diffused from the PUCD matrix. The influence of MCD on the aqueous solubility of several components including steroids has been well documented.[9] A severalfold increase in the solubility of hydrocortisone in water in the presence of MCD has been reported.[9] The increased solubility of hydrocortisone in water in the presence of MCD has been assigned to the formation of an inclusion complex between the MCD and the guest molecule. The remarkably higher values of the diffusion coefficient and the higher solubility of Hy thus could be assigned to MCD present in water that has already diffused from PUCD.

Table III Percent Migration of the Components into Water

Component	Initially Present (mg)	Migrated after 24 h (mg)	% Migration
MCD	16	4	25
Hy (PU)	5.3	0.69	13.02
Hy (PUCD)	4.5	1.23	27.33

The data summarized in the Table III show that the extent of Hy migrated into water from the PUCD matrix is about 27% while the quantity of Hy diffused from PU matrix is about 13%. That is nearly a twofold increase in the solubility of Hy in water is registered by the presence of MCD.

The present study indicates that incorporation of MCD in polymers is a simple approach to enhance the diffusion as well as the availability of hydrophobic components in water. Such polymeric systems may be used to accelerate the release of drugs that are less soluble in aqueous media. Considering the nontoxicity of MCD, such systems may have potential application in the design of polymeric-based release systems.

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